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Intensive blood pressure reduction lowers mortality in CKD

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Abstract

Hypertension is a risk factor for chronic kidney disease (CKD), but the optimal blood pressure (BP) target in patients with stage 3–5 CKD is unclear. Now, a meta-analysis reports that more-intensive BP control is associated with a reduced risk of all-cause mortality compared with less-intensive BP goals in this high-risk population.

Subject categories

Biological sciences; Physiology; Cardiovascular biology; Cardiovascular diseases; Hypertension [URI/631/443/592/75/243]; Health sciences; Diseases; Kidney diseases; Chronic kidney disease [URI/692/699/1585/104] Health sciences; Medical research; Clinical trial design; Clinical trials [URI/692/308/2779/109]

Cardiovascular disease (CVD) is one of the primary causes of death among patients with chronic kidney disease (CKD)[1]. Thus, prevention of CVD is an important priority in the comprehensive care of patients with CKD. As hypertension is a cause of both CKD and CVD, decreasing blood pressure (BP) has the potential to slow CKD progression, prevent CVD events and prolong survival.

A recent meta-analysis by Malhotra *et al.* reports that more-intensive versus less-intensive BP control reduces the risk of all-cause mortality in adults with stage 3–5 CKD (OR 0.86, 95% CI 0.76–0.97)[2] (TABLE 1). The meta-analysis identified 18 trials, including the SPRINT study, that examined the relationship of intensive BP control with mortality in patients with stage 3–5 CKD[2]. In this meta-analysis, all-cause mortality was chosen as the end point because CVD benefits might not translate into improved survival if potential

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Competing interests statement

The authors declare no competing interests.

adverse effects of intensive antihypertensive therapy — such as acute kidney injury (AKI) and syncope — result in death from non-CVD causes.

The findings of the meta-analysis are consistent with those of the SPRINT trial, which tested whether an intensive systolic blood pressure (SBP) goal of <120 mmHg was more effective for primary prevention of CVD than a standard SBP goal of <140 mmHg in a high-risk group of adults without diabetes, including patients with CKD (a subgroup comprising 30% of the participants)[3]. The trial was terminated early because of a reduced risk of both CVD and all-cause mortality in the intensive BP group.

In SPRINT, the benefits of the more intensive BP goal were similar in the CKD and non-CKD subgroups, based on the lack of statistically significant interactions between randomized goal and CKD status. The beneficial effect of intensive BP lowering on all-cause mortality occurred despite a more rapid decline in estimated glomerular filtration rate (eGFR) and an increased incidence of AKI in the intensive compared with the standard BP group[4].

The main finding from this meta-analysis — reduction in all-cause mortality — has important implications for patients CKD?. However, certain caveats exist, with perhaps the most important being potential heterogeneity. Despite statistical evidence of homogeneity (I-squared = 0%), trial results were inconsistent. In fact, 6 of the 18 trials report nonsignificant increases in all-cause mortality in the intensive BP group. It is possible that these effects, which carry less weight in the meta-analysis, are unreliable owing to small sample sizes or low event rates. Similarly, despite nonsignificant interaction tests, some subgroups were small and, strikingly, had null results.

For example, only six trials enrolled patients with CKD and diabetes, and no apparent benefit of intensive BP reduction (OR 0.98, 95% CI 0.78–1.2) was observed. Further exploration of heterogeneity is needed to identify those patients with CKD who will benefit from intensive BP-lowering therapy as well as to plan subsequent trials in subgroups for which the evidence of benefit is uncertain, in particular patients with CKD and diabetes. A second important issue is the relatively short duration of the follow-up period. The median follow-up of trials included in the meta-analysis was only 3.6 years, so potential long-term effects of intensive BP goals could not be examined.

Two trials — the MDRD trial[5,6] and the AASK trial[7] — provide some evidence of extended benefit of intensive BP lowering in patients with CKD. Although the initial trial period of these studies was included in the meta-analysis, the extended follow-up period was not.

MDRD enrolled 840 adults with eGFR of 13–55 ml/min/1.73 m^2, who were randomly assigned to either an intensive or standard BP goal[5]. The intensive BP goal was a mean arterial pressure (MAP) ≤92 mmHg for adults 18–60 years (similar to 125/75 mmHg) or ≤98 mmHg for adults ≥61 years (similar to 145/75 mmHg), whereas the standard BP goal was ≤107 mmHg (similar to 140/90 mmHg) for adults 18–60 years or ≤113 mmHg (similar to 160/90 mmHg) for adults ≥61 years. MDRD documented that the intensive BP goal was associated with a nonsignificant, increased risk of death over a mean of 2.2 years of follow-up (HR 1.37, 95% CI 0.68–2.74). However, extended follow-up (~10 years) revealed that the

intensive BP goal was associated with reduced risk of kidney failure or death (HR 0.77, 95% CI 0.65–0.91)[6].

AASK enrolled 1,094 African-American adults with CKD attributed to hypertension. Participants were randomly assigned to either a MAP goal of ≤92 mmHg (intensive BP group) or a MAP goal of 102–107 mmHg (standard BP group)[7]. No significant between-group difference in death was reported during the trial phase with mean follow-up of 3.8 years (HR 0.75, 95% CI 0.49–1.15). However, over extended follow-up, which ranged from 8.8–12.2 years, intensive BP lowering was associated with a significantly reduced risk of death (HR 0.81, 95% CI 0.68–0.98). Together, MDRD[5] and AASK[7] demonstrate a long-term mortality benefit of intensive BP lowering in CKD, beyond the relatively brief duration of studies included in the meta-analysis.

In conclusion, the results of the meta-analysis by Malhotra *et al.* are consistent with findings from the SPRINT study, which documented increased survival from intensive BP lowering in non-diabetic adults with CKD. Whether these findings apply to adults with diabetes and CKD is uncertain, and trials of intensive versus standard BP goals in this high-risk group are warranted.

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Biography

Lawrence J. Appel is Professor of Medicine, Epidemiology, and International Health at the Johns Hopkins University and Director of the Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, Maryland, USA. The focus of his investigative career is the prevention of cardiovascular and kidney diseases, through both pharmacological and non-pharmacological approaches, often nutrition-based.

Table 1

Key studies that assess the effect of intensive blood pressure goals on mortality in CKD

Study	Population (*n*)	Standard BP goal	Intensive BP goal	Within-trial effects	Post-trial effects	Refs
Meta-analysis by Malhotra *et al.*	Adults with stage 3–5CKD (15,924)	Varied between trials *	Varied between trials *	Reduced risk of all-cause mortality with more-intensive versus less-intensive BP control at a median follow up of 3.6 years (OR 0.86, 95% CI 0.76–0.97)	NA	5
SPRINT trial	Non-diabetic adults with increased risk for cardiovascular events (9361)	SBP: <140mmHg	SBP: <120mmHg	Reduction in all-cause mortality associated with the intensive BP goal in patients with CKD (HR 0.72, 95% CI 0.52–0.93)	NA	3
MDRD trial	Adults with eGFR 13–55ml/min/1.73m^2 (840)	MAP: ≤107 mmHg (18–60 years); ≤113 mmHg (≥61 years)	MAP: ≤92 mmHg (18–60 years); ≤98 mmHg (≥61 years)	Nonsignificant, higher risk of mortality in the intensive BP group (HR 1.37, 95% CI 0.68–2.74)	Reduced risk of kidney failure or mortality in the intensive BP group (HR 0.77, 95% CI 0.65–0.91)	5,6
AASK trial	Non-diabetic African-American adults with hypertensive CKD (1094)	MAP: 102–107mmHg	MAP: ≤92 mmHg	No significant between-group difference in mortality (HR 0.75, 95% CI 0.49–1.15)	Reduced risk of mortality in the intensive BP group (HR 0.81, 95% CI 0.68–0.98)	7

BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure; NA, not available; SBP, systolic blood pressure.

* Median achieved SBP of 130 mmHg in the more intensive groups versus 138 mmHg in the less-intensive groups.

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